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TITLE: Assessment and Rehabilitation of Central Sensory Impairments for Balance in mTBI

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14. ABSTRACT

Objectives: Control of balance requires complex integration of sensory and motor systems. In the clinic or in the field, balance measurement is often over-simplified, preventing balance deficits from being identified and treated after mTBI. Our central hypothesis is that chronic balance deficits after mTBI result from impairments in central sensorimotor integration that may be helped by rehabilitation. There are two objectives of this proposal; the first objective is to characterize balance deficits in people with mTBI. The second objective is to use a novel auditory biofeedback device to improve measures central sensorimotor integration and balance control.

Plan: The proposed 4-year study has two parts: 1) Cross-sectional study (Aim I: Balance Assessment) to identify and characterize maladaptive balance control strategies after mTBI compared to healthy controls and 2) Interventional randomized pilot study (Aim II: Balance Rehabilitation) using a novel auditory biofeedback rehabilitation technique to ameliorate maladaptive balance control strategies after mTBI. Subjects in Aim II will be a subset from Aim I and studies will occur simultaneously.

Methods: I) Balance Assessment: To characterize balance deficits in people with mTBI who have chronic, non-resolving balance deficits compared to healthy control subjects without a history of mTBI. We hypothesize that a) objective measures of central sensorimotor integration, static and dynamic balance will better distinguish people with mTBI from control subjects than clinical measures, b) a subset of people with mTBI will have abnormal central sensorimotor integration test measures, even without peripheral vestibular or ocular motor deficits c) the relationship between poorer static/dynamic balance performance and mTBI is regulated/mediated by central sensorimotor integration. We will test 130 subjects between the ages of 21 and 50; 65 with chronic (> 3 months) mTBI and non-resolving balance deficits and

65 healthy age and gender matched control subjects without a history of mTBI. We will obtain objective measures of static and dynamic balance using wearable inertial sensors and determine how these measures relate to central sensorimotor integration. We will also obtain laboratory measures of peripheral vestibular function and ocular motor function to help classify people and to consider as potential covariates in rehabilitation efficacy.

II) Balance Rehabilitation: To determine the efficacy of a novel, auditory biofeedback balance rehabilitation program to improve central sensorimotor integration, static and dynamic balance, and functional activity in patients with chronic mTBI. We hypothesize that a) central sensorimotor integration scores will improve with rehabilitation and auditory biofeedback will increase the improvement of central sensorimotor integration scores beyond the standard of care, b) auditory biofeedback intervention will improve objective summary measures of balance and c) people with central sensorimotor integration impairment will show sustained improvement in central sensorimotor integration scores and balance after rehabilitation. We will randomize 40 subjects between the ages of 21 and 50; 65 with chronic (> 3 months) mTBI and non-resolving balance deficits from Aim I who have abnormal central sensorimotor integration into either the auditory biofeedback rehabilitation group or the standard of care group. People will be tested before and after a 6-week intervention period and again 6 week later to determine long-term changes. Normal/abnormal vestibular and ocular motor function will be used as covariates to determine if peripheral deficits affect the efficacy of auditory biofeedback rehabilitation.

Relevance to VA's Mission: These proposed studies have the potential to change the way in which military personnel are assessed and rehabilitated after mTBI. When this project is completed, we expect to have shown that central sensory integration for balance control is impaired in people with chronic mTBI. We will demonstrate how portable, body-worn sensors can be used to characterize problems and rehabilitate balance using novel auditory biofeedback. Findings from this research can be very readily adopted into military balance screening in the field post mTBI as well as for better military and civilian balance rehabilitation.

Findings to Date: We have tested 17 control subjects and 1 subject with mTBI on the protocol, including all questionnaires and tests of cognition, vestibular function, sensory motor integration and gait and balance. One additional subject with mTBI completed the questionnaires, tests of cognition and vestibular function evaluation. Our findings to date will help establish normative values as we begin to recruit more mTBI subjects in the upcoming year. Our current enrollment includes 8 men, 11 women with a mean age of 26.4 years. Fifteen people reported ethnicity as non-hispanic/Latino and 4 as hispanic/Latino. Seventeen people reported as white, 1 as more than 1 race and 1 as unknown. Only descriptive analysis has been performed on the data; no further analysis has been performed to date.

Medical Subject Heading (MeSH) terms: Balance, mTBI, Rehabilitation

15. SUBJECT TERMS

Balance, mTBI, Rehabilitation, Brain Injury, BESS, Dynamic Posturography, SOT, Inertial Sensors, Balance, Auditory Biofeedback, Central Sensory Integration, Concussion					
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KEYWORDS: mTBI, Rehabilitation, Brain Injury, BESS, Inertial Sensors, Balance, Auditory Biofeedback, Central Sensory Integration, Concussion

ACCOMPLISHMENTS:

- ***What were the major goals of the project?***

Goal	Target Completion Date	Percentage of Completion/ Date of Completion
Specific Aim 1 (Study 1: Assessment n=130 mTBI)		
Major Task 1: Launch Study Activities	*30-Feb-2016*	95%
Major Task 2: Recruitment and Testing (n=130)	*30-Feb-2019*	15%
Major Task 3: Data Analysis and Publications	*30-Sep-2019*	5%
Specific Aim 2 (Study 2: Rehabilitation n=40 mTBI)		
Major Task 1: Launch Study Activities	*30-Feb-2016*	95%
Major Task 2: Prepare Technology and Protocol for Intervention	*30-Sep-2016*	100%
Major Task 3: Randomized Interventions (n=40 mTBI)	*30-Feb-2019*	5%
Major Task 4: Assess Efficacy of Interventions (n=40)	*30-Feb-2019*	0%
Major Task 5: Data Analysis and Publications	*30-Sep-2019*	0%

❖ ***What was accomplished under these goals?***

Status of major activities and specific objectives:

Specific Aim 1 (Study 1: Assessment n=130)

Major task 1: Launch study activities

Subtask 1: Prepare regulatory documents and research protocol

- Set up sub award between sites; 100% complete *06-Jan-2016*.
- Finalize consent form and human subject protocol; refine eligibly criteria, exclusion criteria and screening protocol; 100% complete *24-Aug-2015*.
- Prepare testing protocol for both sites; protocols have been established at each of the test locations but these protocols are still awaiting the VA Neurocom fix. Vestibular testing has been done at both the VA and OHSU; 95% complete.
- Prepare screening and testing forms for subject database; 100% complete *09-May-2016*.
- Prepare combined OHSU/VA IRB documents; 100% complete *27-Oct-2015*.
- Prepare FITBIR forms for data reporting; the majority of forms have been published. Drafts for the Modified BESS, Bucket and Proprioception Tests have all been created and we are awaiting publication. Data elements for the Short Blessed Test, Pain Location Inventory, Symptom Impact Questionnaire and Modified CTSIB have been created and the forms are under development. We are actively working with someone at FITBIR to create forms for our study specific tests, including the CSMI test and Dual-task walking test; 60% complete.

Subtask 2: Prepare technology for study

- Modify SOT platform for new CSMI test; platforms have been modified and are installed in each of their finalized locations. The modification of the Neurocom balance platform for the purpose of performing the CSMI testing has been complete at the OHSU site. However, the CSMI test at the Portland VA has not been complete due to a malfunctioning software update. We have contacted the company and are awaiting help from them. The electrical components (circuit cards that support body sway recordings, power supply, electrical connections) have been designed and are in place; 95% complete.
- Purchasing and testing software of Opals; awaiting release of newer, updated sensor from APDM to determine need for more sensors for at-home data collection; 90% complete.
- Validate CSMI on commercial Neurocom SOT compared to laboratory posturography; 100% complete *01-Jul-2016.*
- Develop new algorithm to automatically quantify head movements from Opal sensor; 100% complete *23-Sep-2016.*
- Set up and test gait paradigm with turns and dual task; 100% complete *23-Sep-2016.*
- Dual task; test microphone for recording cognitive task; 100% complete *27-Jun-2016*.

Subtask 3: Hiring and training personnel

- Hire RA at the VA; 100% complete *01-Jan-2016*.

- Staff completes research compliance training; 100% complete *24-Aug-2015*.
- Train VA audiologist and RA in data collection; 100% complete *03-May-2016*.

Subtask 4: Research essential documents

- HRPO approval for human protocol; 100% complete *18-Dec-2015*.

Subtask 5: Study registration (Not included in original SOW)

- Complete the Clinical Trial Registry; 100% complete *29-Mar-16*
- Complete registration for FITBIR; 100% complete *15-Mar-2016*.

Major Task 2: Recruitment and testing (n=130)

Subtask 1: Recruitment (n=130)

- Prepare brochures for subject recruitment and meet with primary sources of referral; fliers have been approved by our IRB. We are now working with Dr. Chesnutt's clinic and Epic records for further recruitment. We will have research assistants reach out to other local clinics who treat patients with mTBI to post fliers and spread awareness of the study; 60% complete.
- Finalize recruitment strategy; 100% complete *30-Aug-2016.*
- Phone screening of subjects; screenings are being performed at both OHSU and the VA. A telephone recruitment and screening script has been approved by our IRB. This will be an ongoing procedure in the protocol; 10% complete.
- Schedule vestibular/audiogram/ocular motor, CSMI, balance and gait testing; 20% complete.

Subtask 2: Data collection/management (n=130)

- Schedule testing sites for data collection; subjects are currently being scheduled for their vestibular/audiogram/ocular motor testing at both OHSU and the VA. Subjects are being scheduled for the CSMI, balance and gait testing at the OHSU location currently. We are waiting to begin scheduling at the VA until the Neurocom software is fixed; 20% complete.
- Data collection for the 2 days of data collection for aim 1 takes place; subjects are currently being scheduled for vestibular testing at both sites, and for CSMI, balance and gait testing at the OHSU location. We are awaiting VA testing site completion based on Neurocom software; 15% complete.
- Data back-up onto server including manual data entry; REDCap database setup complete and backup server setup. We have verified both servers and will continue to enter and back up data; 15% complete.
- Screen and verify data on server; check for accuracy; these data check will be performed quarterly; 15% complete.
- Upload data to FITBIR; we have submitted data for all published forms, for all subjects tested so far. We will continue uploading our current data, as more forms become published. Going forward, we will upload data quarterly, in accordance with FITBIR's reporting guidelines; 10% complete.

Major Task 3: Data analysis and publications

Subtask 1: Data analysis

- Perform all analysis according proposal and share all findings with investigators; we have begun descriptive analysis with the data collected to date. Further analysis will be conducted as more data is collected; 5% complete.

Subtask 2: Manuscripts and presentations

- Disseminate findings (abstracts, presentations, papers, DoD); this study has been registered at ClinicalTrials.gov, a site available to the public. The PI and postdoctoral fellow just recently presented the protocol of this project at the TBI Symposium: From Research to Recovery on September 16th and 17th, 2016, an event sponsored by the Oregon Brain Institute and OHSU. A paper on the protocol is currently in progress as well; 5% complete.
- Integrate new protocols and head movement metrics into APDM mobility lab system; 0% complete.

Specific Aim 2 (Study 2: Rehabilitation n=40 mTBI)

Major Task 1: Launch study activities

Subtask 1: Hire and train personnel

- Hire and train physical therapists for intervention; 100% complete *26-Aug-2016.*
- Order ABF and exercise equipment; 100% complete *08-Mar-2016*.

Major Task 2: Prepare technology and protocol for intervention

Subtask 1:

- Finalize and prepare written protocol for PT training; 100% complete *26-Aug-2016.*
- Test 2 ABF devices with new protocol; 100% complete *26-Aug-2016.*
- Train ABF PT in protocol; 100% complete *26-Aug-2016.*
- Interpretation of CSMI for each mTBI subject provided to PT to design intervention; after discussing feasibility, the PT will not receive CSMI information and the program will be standardized for all subjects; 100% complete *26-Aug-2016.*

Major Task 3: Randomized interventions (n=40 mTBI patients)

Subtask 1:

- Statistician prepares randomization schedule; 100% complete *9-Sep-2016.*
- PTs call subjects to schedule intervention; rehabilitation program has been finalized and subjects are ready to be scheduled. We will begin to focus on recruitment for Aim 2 in the next quarter; 5% complete.
- 6 week interventions at both sites; for the ease of PT and PT team members, all interventions will take place at OHSU. We will begin to focus on recruitment for Aim 2 in the next quarter, 0% complete.
- PTs document compliance, adverse events and progression of exercise for each subject; all forms have been created and entered in database and are ready for use; 5% complete.

Major Task 4: Assess efficacy of interventions (n=40)

Subtask 1:

- Immediate post-test after intervention; one subject has been enrolled in this aim yet. Recruitment efforts will be increased in the next quarter; 0% complete.
- Long-term assessment 6 weeks later to assess retention of improvements; no subjects have been enrolled in this aim yet. Recruitment efforts will be increased in the next quarter; 0% complete.

Subtask 2:

- A subset of controls will be tested at a 6 week follow up in order to determine any natural changes in the CSMI test over 6 weeks; five control subjects have already been assessed and we plan to test 10 subjects; 50% complete.

Major Task 5: Data analysis and publications

Subtask 1: Data Analysis

- Perform all analysis according proposal and share all findings with investigators; 0% complete.

Subtask 2: Manuscripts and presentations

- Disseminate findings (abstracts, presentations, papers, DoD), including American Physical Therapy Association and American Congress of Rehabilitative Medicine and rehabilitation journals to share with clinicians; this study has been registered at ClinicalTrials.gov, a site available to the public. The PI and postdoctoral fellow just recently presented the protocol of this project at the TBI Symposium: From Research to Recovery on September 16th and 17th, 2016, an event sponsored by the Oregon Brain Institute and OHSU; 5% complete.
- Publish novel ABF intervention protocol; a paper on the protocol of this project has been submitted to BMC Neurology and is under review; 50% complete.

Significant Results/ Key outcomes:

Please note that the data reported and compiled below is as of September 29th, 2016. From that date to now (October 20th) we have enrolled and tested 2 more people with mTBI and 2 more control subjects and their data will be included in the next report.

Table 1. Demographics. Research assistants administer a series of questions during the screening process to determine this information.

Type		Gender		Average Age
Control	mTBI	Male	Female	26.39
17	2	8	11	

Ethnicity			Race						
Hispanic/ Latino	Not Hispanic/ Latino	Unknown/ Not reported	American Indian/ Alaska Native	Asian	Black/ African American	More than one race	Native Hawaiian/ Other Pacific Islander	Unknown/ Not reported	White
4	15	0	0	0	0	1	0	1	17

Table 2. Screening/Questionnaires. Research assistants review and administer the following questionnaires with each subject.

Test		Controls (n=17)	mTBI (n=2)
		Average ± SD	Average ± SD
Short Blessed Test		0.65 ± 1.27	0 ± 0
SCAT-3	# of Symptoms (22)	2.06 ± 4.02	10.50 ± 0.71
	Severity (132)	2.76 ± 5.92	25.50 ± 2.12
PTSD Checklist		22.29 ± 10.07	61 ± 14.14
Neurobehavioral Symptom Inventory		4.06 ± 5.32	38.5 ± 2.12
Short Form 36 – General Health		81.47 ± 14.00	37.5 ± 10.61
Pain Location Inventory		0.41 ± 0.62	13 ± 8.49
Symptom Impact Questionnaire		10.41 ± 10.19	56 ± 0
Beck's Depression Inventory		2.47 ± 2.90	32 ± 1.41
Dizziness Handicap Inventory		0.12 ± 0.49	4.00
ANAM Composite Score		0.24 ± 0.58	0.69

Table 3. Vestibular Data. Collection of vestibular data is conducted in the vestibular lab by an audiologist, under the direction of Dr. Tim Hullar.

Test		Controls (n=17)	mTBI (n=2)
		Average ± SD	Average ± SD
Video Head Impulse Test (vHIT)	Right Horizontal Gain	0.96 ± 0.07	1.00 ± 0.02
	Left Horizontal Gain	0.87 ± 0.15	0.92 ± 0.04
	Symptom Score: Headache	0.14 ± 0.53	0 ± 0
	Symptom Score: Dizziness	0.14 ± 0.53	0 ± 0
	Symptom Score: Nausea	0 ± 0	0 ± 0
cVEMP	Right Amplitude	156.42 ± 63.38	Absent & 181.98
	Left Amplitude	165.32 ± 81.53	127.32 ± 88.14
	Asymmetry Ratio	19.44 ± 22.88	51 ± 69.30
	Symptom Score: Headache	0 ± 0	0 ± 0
	Symptom Score: Dizziness	0 ± 0	0 ± 0
	Symptom Score: Nausea	0 ± 0	0 ± 0
oVEMP	Right Amplitude	12.64 ± 7.68	Absent & 9.94
	Left Amplitude	15.20 ± 10.57	Absent & 11.66
	Asymmetry Ratio	31.09 ± 26.67	N/A & 8
	Symptom Score: Headache	0 ± 0	1.5 ± 2.12
	Symptom Score: Dizziness	0 ± 0	3 ± 0
	Symptom Score: Nausea	0 ± 0	0 ± 0

Convergence	Trial 1	2.64 ± 2.04	6.25 ± 6.72
	Trial 2	3.28 ± 3.20	5.50 ± 6.36
	Trial 3	3.38 ± 3.89	5.25 ± 6.01
	Symptom Score: Headache	0 ± 0	1 ± 1.41
	Symptom Score: Dizziness	0 ± 0	0 ± 0
	Symptom Score: Nausea	0 ± 0	1 ± 1.41
Calorics	Right Warm SPV	21.88 ± 19.10	34.00 ± 11.31
	Left Warm SPV	18.88 ± 10.92	27.50 ± 2.12
	Right Cold SPV	18.41 ± 12.05	21.00 ± 5.66
	Left Cold SPV	17.41 ± 9.84	18.50 ± 0.71
	Unilateral Weakness	19.31 ± 15.13	9.00 ± 11.31
	Symptom Score: Headache	0.53 ± 2.18	1.5 ± 2.12
	Symptom Score: Dizziness	2.00 ± 2.65	1.5 ± 2.12
	Symptom Score: Nausea	0.47 ± 1.70	2 ± 0

Table 4. Motor Tests. A series of tests to assess motor function, static and dynamic balance, and central sensory integration are conducted by the research assistants, under the direction of Laurie King, principal investigator, Peter Fino, post-doctoral fellow, and Robert Peterka, co-investigator. While performing the Modified Clinical Test of Sensory Interaction in Balance (mCTSIB), Modified Balance Error Scoring System (mBESS) and walking tests, subjects wear five Opal inertial sensors (APDM, Inc) on: both feet, chest, forehead and posterior trunk at the level of L5 with elastic Velcro bands. Inertial sensor data was collected at 128Hz and wirelessly streamed to a laptop for automatic generation of gait and balance metrics by Mobility Lab software (APDM, Inc). In the mCTSIB and mBESS tests, clinical instructions are followed. In the walking test, subjects are asked to walk for approximately four minutes. The test is performed first, with, and then without an auditory Stroop device. Selected metrics are presented in the table below to give an overview of the data.

Test		**Controls (n=17)**	**mTBI (n=1)**
		Average ± SD	Average
Reaction Time Test	Reaction Distance	21.80 ± 4.09	21.5
	Reaction Time	0.21 ± 0.02	0.21
Bucket Test	Left	-1.55 ± 2.31	-1.4
	Right	0.05 ± 2.08	-13.5
	Both	-0.18 ± 2.56	-13.7
	All	-0.62 ± 2.11	-9.5
Proprioception		0 ± 0	0
Sensory Orientation Test (SOT)	Condition 1	93.78 ± 2.33	95
	Condition 2	90.49 ± 3.59	92.67
	Condition 3	89.88 ± 4.79	92.67
	Condition 4	76.84 ± 14.81	77.33
	Condition 5	67.36 ± 13.57	56.00
	Condition 6	65.42 ± 17.66	43.67

	Composite	75.18 ± 10.38	71.00
Modified CTSIB		120 ± 0	120
mBESS Test	Total Score	3.10 ± 4.37	5.00
	RMS Coronal Sway Acceleration (Feet Together, Eyes Closed, Firm Surface)	0.057 ± 0.019	0.039
Stroop Test	Accuracy	98.40 ± 1.55	99
	Response Time	0.84 ± 0.16	0.96
Long Walk	Gait Speed	1.21 ± 0.13	1.25
	DST	18.92 ± 2.04	18.92
	Lateral Step Variability	2.95 ± 0.62	3.77
	Trunk Coronal ROM Mean	3.78 ± 1.69	6.35
	Trunk Coronal ROM Variability	0.79 ± 0.38	0.69
	Turn Duration	1.91 ± 0.23	2.35
	Turn Velocity	218.49 ± 36.19	173.3

CSMI Test Description.

The goal of CSMI testing is to provide a set of functionally meaningful parameters that define behavioral characteristics of the balance control system and quantify how these characteristics are modified to account for changing environments and challenges to balance. The CSMI test evokes body sway responses to stimuli consisting of pseudorandom rotations of either the stance surface (eyes closed and eyes open conditions), the visual surround, or both with each test condition performed at 2 different amplitudes. The stimulus-response data are analyzed using system identification methods to calculate frequency response functions (FRFs) that characterize the frequency-dependent magnitude (gain) and timing (phase) of body sway evoked by each stimulus and thus define the dynamic characteristics of the balance control system. Parameters of a mathematical feedback control model of the balance system are then adjusted so that the model-predicted FRFs optimally match the experimentally determined FRFs. Model parameters are obtained from each subject on each individual test trial, and these parameters are the basis for making comparisons between mTBI and control subjects and among different mTBI subjects.

CSMI tests are performed using the Research Module on a modified Balance Manager platform (Neurocom International, Inc.). The modification added an apparatus (mounting frame, motion sensors, and interface electronics) that provides a direct continuous measure of sway at two points on the body for calculation of the time course of body center of mass (CoM) motion in response to the various pseudorandom stimuli. The stimulus protocols and apparatus modifications have been completed at both sites (OHSU and VA NCRAR).

CSMI Test Results.

Normative data has been collected and analyzed. Results from CSMI testing are described and are presented in the form of example individual FRFs from control subjects in 2 of the 8 test conditions. Balance control model parameters were estimated from each subject's FRF in each of the 8 CSMI tests.

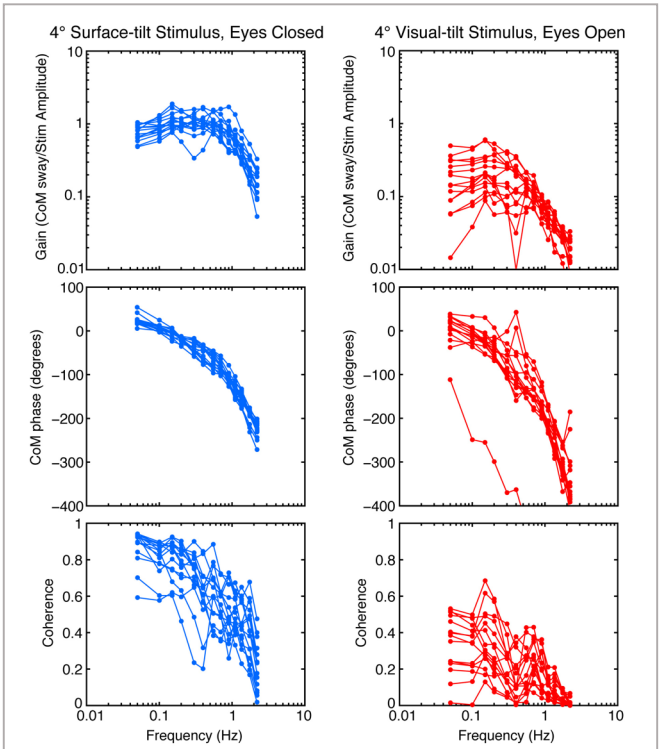


Figure 1. *Frequency response functions and coherence functions of 15 control subjects in 2 of the 8 CSMI tests.*

Figure 1 (left column) overlays the FRFs from the 15 control subjects in the surface tilt, eyes closed, 4° amplitude test. The FRFs consist of gain and phase curves as a function of stimulus frequency. Additionally, coherence functions for each subject are shown. Coherence function values can range from 0 to 1 with larger values indicating greater signal-to-noise ratios meaning that the responses at a particular stimulus frequency show little cycle-to-cycle variation, and thus indicates reliable data quality. The coherence results in the condition shown in **Fig. 1** (left column bottom plot) show fairly large values indicating reliable experimental results from individual subjects. Coherence results were similar across the other test conditions with the exception of tests that presented visual surround tilts during stance on an unmoving surface where coherences were lower due to the fact that subjects were less responsive (have lower gains) to visual stimuli than surface stimuli (**Fig. 1**, right column). Nevertheless, FRF gain and phase measures from visual stimuli were reliable enough in almost all subjects (i.e., showed consistent and expected changes in gain and phase across frequency) to allow for reliable estimates of balance control parameters. Additionally, low average coherence values can and will be used as an indicator of low quality data so that model parameters obtained from low quality data are not used in evaluating the sensorimotor function of mTBI subjects.

Balance control parameters are estimated by fitting equations, based on the model showing in **Fig. 2** to the experimental FRF data. There are 5 parameters (**Fig. 2**) obtained from fits to each of the 8 experimental tests for each individual subject.

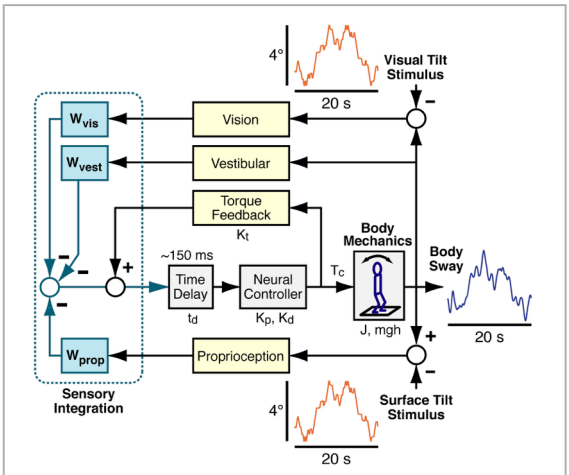


Figure 2*. Block diagram of model used in the identification of parameters that characterize the balance control system.*

The parameters include: 1. Sensory weight factor, 2. Neural controller stiffness factor (K_p), 3. Neural controller damping factor (K_d), 4. Time delay (t_d), and 5. Torque feedback gain factor (K_t). All parameters are being evaluated to identify balance control characteristics that could potentially give insights into balance deficits in mTBI subjects. But current and preliminary results indicate that the sensory weights and neural controller parameters are the most likely parameters to identify pathological balance function caused by mTBI.

The sensory weight factor provides an estimate of the proportion of sensory information from proprioception (W_{prop} in tests using surface-tilt stimuli), from vision (W_{vis} in tests using visual-tilt stimuli), or from both proprioception and vision (W_{prop}+W_{vis} in tests using simultaneous surface-visual-tilt stimuli) that a subject is using for balance control.

The neural controller parameters quantify the sensory-to-motor transformation that converts combined sensory orientation information into a motor response (corrective ankle torque). Both of these parameters would be expected to scale in relation to body dimensions and therefore are normalized by *mgh* which defines the magnitude of disturbance torque due to gravity acting on the body for body tilts away from vertical) where *m* is body mass, *g* is the gravity constant, and *h* is the CoM height above the ankle joint.

Figure 3 shows plots of sensory weight and normalized neural controller parameters for the 8 experimental tests. The x-axis label applies to all plots and identifies the stimulus conditions for the 8 tests. Mean parameter values are plotted with error bars indicating ±1 standard deviation. The data from the single mTBI subject tested to date are plotted with connecting lines.

Results for control subjects follow the patterns expected from previous studies. Proprioceptive weights, W_{prop}, identified using surface-tilt stimuli, were larger with eyes closed compared with eyes open. Visual weights, W_{vis}, identified using visual-tilt stimuli, had small values indicating the visual orientation cues made a relatively small contribution to balance control compared to orientation information from other sensory systems during stance on a fixed and level surface.

For neural controller properties, the normalized stiffness, K_p/mgh, and damping, K_p/mgh, parameters do not change markedly across test conditions. K_p/mgh values are greater than 1 as they must be for

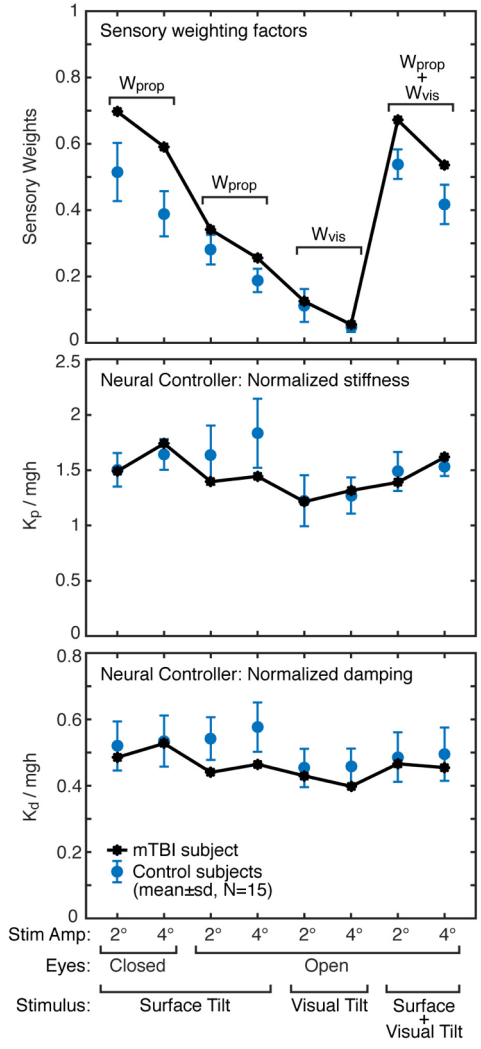


***Figure 3**. Mean (±sd) model parameter values of control subjects and an individual mTBI subject.*

stable balance control since the corrective torque generated by the balance system has to be greater than the disturbance torque due to gravity.

Results for an mTBI subject that show a specific pattern of abnormal results. For sensory weights the general pattern was for W_{prop} values to be considerably greater than control subjects. Similarly, the mTBI subject's W_{prop}+W_{vis} values from the surface plus visual-tilt test conditions were greater than any of the individual control subject values. In both of these test conditions, the vestibular system is the other contributor to balance control and thus implies that this mTBI subject was less able to use vestibular orientation information for balance control than control subjects. Reduced vestibular utilization could be due to a peripheral vestibular deficit or to a central deficit in sensory integration. In contrast the mTBI subject showed a normal ability to use visual information for balance control (center normal W_{vis} values).

Neural controller parameters for the mTBI subject also showed deviation from control subject results where, mainly in the eyes open surface-tilt stimulus condition, normalized K_p and K_d values were lower than nearly all of the individual values from control subjects. Low values of K_p and K_d indicate the subject was generating less corrective torque in this specific test condition. In this particular mTBI subject's case, the subject's greater reliance on proprioceptive information for balance in combination with reduced corrective torque generation in conditions where visual information is available makes the subject particularly vulnerable the balance disturbances caused by surface movement.

These early results demonstrate that CSMI testing can reveal sensorimotor abnormalities associated with mTBI that are clearly distinguishable from control subjects.

- ***What opportunities for training and professional development has the project provided?***

Dr. Laurie King attended the Military Health System Research Symposium in Kissimmee, Florida, August 2016 and presented the preliminary work that this project was founded on. During this meeting she was able to meet with several other scientists with overlapping interests and collaborations were discussed. The PI was also able to attend two local conferences that addressed the issues of sensory motor integration and gait and balance assessment. She attended the 6th International Symposium on Gait and Balance in Multiple Sclerosis, September 9th-10th, 2016, and the World Parkinson Congress, September 20-23, 2016. These conferences involved discussions with internationally known speakers regarding the role of vestibular and proprioceptive information on gait and balance, which are central themes of the current project.

Peter Fino, post-doctoral fellow on the study, attended the Biomechanics and Neural Control of Movement Conference from June 12th-17th, 2016 at the Deer Creek Lodge in Mt. Sterling, Ohio. This conference involved intimate discussions of neural feedback control, motor coordination strategies, rehabilitation goals, and motor learning paradigms with goals of 1) identifying progress within the past 20 years and 2) outlining a research path for the next 20 years. Peter attended this meeting to meet with world leaders in sensory feedback control, a key domain to

the current grant. At the meeting, Peter gained knowledge about neural control mechanisms and applications to gait and balance that will benefit the project.

Members of study team attended the second annual TBI Symposium: From Research to Recovery on September 16th and 17th, 2016, to gain knowledge in both the current research as well as the clinical approaches to accurately diagnose and treat concussions. Peter Fino and Dr. Laurie King both presented our current project and the most up-to-date findings at this symposium. Additional team members were able to attend.

- ***How were the results disseminated to communities of interest?***

We have registered this trial at ClinicalTrials.gov, which is available to the public. At this site potential subjects can get information about the study as well as contact the study team to participate as either a healthy control or mTBI if they are eligible.

As mentioned above, the post-doctoral fellow, Peter Fino, and the PI, Dr. Laurie King, presented the protocol of this research at the TBI Symposium: From Research to Recovery, an event sponsored by the Oregon Brain Institute and OHSU, on September 16th and 17th, 2016. This seminar was available to scientists, clinicians and the public, and greatly impacted the base of knowledge and understanding of mTBI.

Members of the study team co-authored and submitted a manuscript on the protocol of this project, titled 'Assessment and Rehabilitation of Central Sensory Impairments for Balance in mTBI using Auditory Biofeedback: A Randomized Clinical Trial,' to BMC Neurology. The paper was submitted on October 11, 2016 and is currently under review.

- ***What do you plan to do during the next reporting period to accomplish the goals?***

The main focus for this next quarter will be the recruitment of mTBI subjects, data collection and hiring a postdoctoral fellow for preliminary data analysis. Now that we have a recruitment strategy, fliers and a phone script we will begin implementing this strategy to recruit mTBI subjects through primary sources of referral. We will continue contacting and recruiting subjects using referrals and medical record screening throughout the next year. Once we receive the software update for the Neurocom we will begin testing subjects at the VA site as well. We plan to continue collecting data for both healthy control subjects until we have reached n=65 and mTBI until n=65. We plan to collect 6-week follow-up testing for 5 more healthy control subjects to meet our goal of 10. As we continue to enroll mTBI subjects we will randomize them into the two treatment groups. We plan to integrate and develop the new ABF protocol as we enroll more subjects in this protocol. As we collect more data, our new post doctorate fellow will begin processing data and preparing analysis for publication and presentation. At that time, we will assess the efficacy of interventions and start publishing our results.

IMPACT:

- ***What was the impact on the development of the principal discipline(s) of the project?***

This project will impact the base of knowledge and theory of Physical Therapists who work with people who suffer from TBI and associated chronic balance deficits. This project will give insight into a novel approach to treat this population using auditory biofeedback. The treatment and practice of physical therapy will likely be impacted by this research and may shift the standard of care to integrate audio biofeedback therapy. Clinical practice is likely to be impacted through the implementation of wearable sensors to more accurately measure and assess gait and balance, during both at-home activity, as well as in clinical and rehabilitative settings.

- ***What was the impact on other disciplines?***

We are working with two sites to consolidate testing of vestibular function in chronic TBIs. This has expanded the base of knowledge for each of these sites to include oculomotor, vestibular and reaction time tests. As a result, this project will likely impact the techniques and protocols used in this field.

- ***What was the impact on technology transfer?***

Nothing to Report

- ***What was the impact on society beyond science and technology?***

We are expanding and improving public knowledge on TBIs using a variety of methods, including presenting at symposiums, meeting with physicians and physical therapists, engaging in direct discussion with patients and their families and distributing fliers. Through these interactions this project will likely impact the perception of chronic balance problems in TBIs. This will likely have a positive impact on patients, their families and health care professionals, to adequately seek and offer treatment for balance problems.

CHANGES/PROBLEMS:

- ***Changes in approach and reasons for change***

Nothing to Report

- ***Actual or anticipated problems or delays and actions or plans to resolve them***

Testing subjects at the VA may continue to be a delayed because we are awaiting software for the Neurocom. When CSMI data is collected using the Research Module of the Neurocom software, the data needs to be 'Exported' by the Neurocom software before it can be read and analyzed by our custom Matlab software. The CSMI testing collects data from our sway rods to measure body displacement using 2 auxiliary channels in the Neurocom system. Unfortunately, the software version running the VA Neurocom (which is the latest version available from Neurocom) has an error that does not allow for the export of data collected using the extra auxiliary channels. Neurocom was informed of this error in April 2016 and they acknowledge that it is in fact an error in their software. They have promised that this error will be fixed in the

"soon-to-be-released" update of their software. They originally indicated the software update would be released by the end of June, but that did not happen and we still do not have updated software that fixes their error. However, we have verified that data collected with the auxiliary channels is being collected correctly, and it is only the export function that is defective. Therefore, we are able to collect CSMI data on the VA Neurocom, but we will not be able to analyze it until the new Neurocom software version is released.

Of note, the OHSU Neurocom platform is running an older version of the Neurocom software on an older version of Microsoft Windows. The export function does work correctly with that older Neurocom software. However, it is not practical to revert the VA Neurocom back to using older software due to other ongoing studies that use the VA Neurocom. We have been in contact with the company and they are working to get us this software. Once the software has been implemented the machine will need to be validated with Dr. Robert Peterka's platform before testing subjects at this site.

Since we only began data collection in June 2016, we do not have enough data to assess the efficacy of the interventions or complete thorough data analysis. To date, we have not had any mTBI subjects in the intervention group and cannot document compliance with protocol. We purposely did not start recruiting mTBI until the protocol for Aim 2 was finalized. This included completing the rehabilitation protocol, purchasing supplies for rehab and becoming familiar with the audio biofeedback system. We also did not start recruiting mTBI until the study personnel collecting data felt confident with equipment, setup and protocol. Now that all study personnel have been trained and are comfortable conducting tests with healthy controls, we will begin targeting recruitment efforts at subjects with mTBI. We plan on achieving this by having the Research Assistants collaborate with Dr. Jim Chesnutt and other OHSU family/sports medicine physicians who treat subjects with mTBI, to attend clinics and recruit potential subjects. Drs. Andrea Karl and Shiny Vergis, who work at the TBI/Polytrauma Support Clinic at VAPORHCS have agreed to help identify potential subjects in their clinic as well. RAs will reach out to concussion clinics in the surrounding area, to post fliers and spread awareness of the study. Potential subjects are currently being identified through the Comprehensive TBI Evaluation database online, and contacted via recruitment letter (as soon as IRB approval is obtained) or by an RA directly. Informational fliers will be posted around the VA and OHSU in high traffic areas and in departments that treat mTBI. RAs will ensure fliers are present at any related outreach events in the community.

We are currently hiring for a postdoctoral fellow to work solely on this project. We have received qualified applications and are processing them at this time, with the goal of hiring for this position by the end of the year.

- ***Changes that had a significant impact on expenditures***

Due to late start-up, most personnel did not have effort on this project until December 2015. This created some savings in the year 1 budget. We are using these savings to hire a full-time postdoc in Year 2. We also recently hired two Research Assistants now that our project is up to speed.

In addition, we have not received invoices from the VA for their employees September 2016 efforts. This will increase the total expenditures that we have listed in the quad chart once we have received and paid the invoices.

- ***Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents***

Nothing to Report

PRODUCTS:

- Presentation of protocol and up-to-date findings at the TBI Symposium: From Research to Recovery, September 16th and 17th, 2016 at OHSU
- Journal publication – Peter C Fino, Robert J Peterka, Timothy E Hullar, Fay B Horak, James C Chesnutt, Laurie A King; Assessment and Rehabilitation of Central Sensory Impairments for Balance in mTBI using Auditory Biofeedback: A Randomized Clinical Trial; BMC Neurology; submitted and under review; Federal support was acknowledged.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS:

- ***What individuals have worked on the project?***

Name:	*Laurie King*- No Change

Name:	*Fay Horak*- No Change

Name:	*Jim Chesnutt*- No Change

Name:	*Timothy Hullar*- No Change

Name:	*Robert Peterka*- No Change

Name:	*Edward King*- No Change

Name:	*Sean Kampel*- No Change

Name:	*Marco Juardo*- No Change

Name:	*Shelia Markwardt*- No Change

Name:	*Sam Gordon*- No Change

Name:	*Peter Fino*
Project Role:	*Post-doctoral Fellow*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Dr. Fino has performed work in the design, collection, and processing of static and dynamic balance data.
Funding Support:	

Name:	*Merissa Walls*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Ms. Walls has performed work in coordination of study events, data collection and data entry.
Funding Support:	

Name:	*Emily Sippel*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	

Nearest person month worked:	2
Contribution to Project:	Ms. Sippel has performed work in collection of data, assisting in study intervention and data entry.
Funding Support:	

Name:	*Heather Belding*
Project Role:	*Research Assistant*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.75
Contribution to Project:	Ms. Belding has performed work in the recruitment of mTBI subjects from the VA, data collection and data entry.
Funding Support:	

- ***Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?***

Nothing to Report

- ***What other organizations were involved as partners?***

Nothing to Report

SPECIAL REPORTING REQUIREMENTS:

See Quad Chart attached

Assessment and Rehabilitation of Central Sensory Impairments for Balance in mTBI

PI: Laurie King, PhD, PT **Org: Oregon Health & Science University** **Award Amount:$1.9 million**

Veteran Affair Portland Health Care System

Study/Product Aim(s)

Our hypothesis is that chronic balance deficits after mTBI result from central sensorimotor impairments that can be quantified and improved by rehabilitation.

I) To characterize balance deficits in people with mTBI who have chronic, non-resolving balance deficits compared to healthy control subjects without a history of mTBI.

II) To determine the efficacy of a novel, audio biofeedback (ABF) balance rehabilitation program to improve central sensorimotor integration, static and dynamic balance and functional activity in patients with chronic mTBI.

Approach

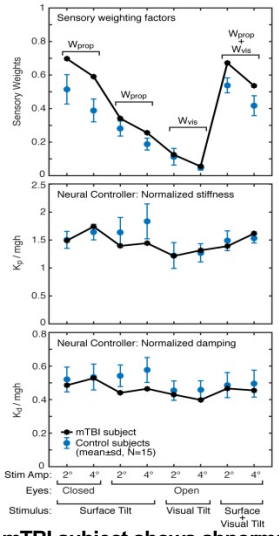
Study I (*Balance Assessment*): We will test 65 control and 65 mTBI subjects with chronic balance deficits (with and without vestibular and/or ocular motor deficits) using novel, instrumented, objective measures of balance including postural sway (static), gait variability (dynamic) and central sensorimotor integration.

Study II (*Balance Rehabilitation*): We will randomize 40 people with chronic (>3 months) balance deficits from mTBI into either ABF based rehabilitation or standard of care rehabilitation for balance control.

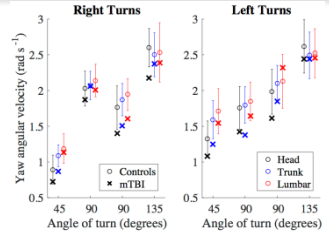
Timeline and Cost

Activities CY	16	17	18	19
IRB, Hiring, Training, Purchasing				
Recruitment				
Aim I: Balance Assessment 65 Control; 65 mTBI				
Aim II: Balance Rehabilitation 40 Randomized mTBI				
Data analysis				
Manuscript Preparation and Submission				
Estimated Budget ($K)	$533	$475	$486	$499

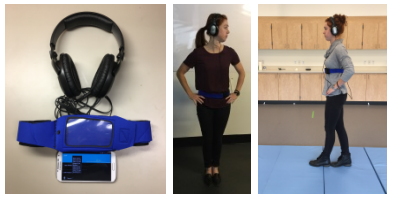
Updated: Portland, OR; 29 September 2016



Single mTBI subject shows abnormal use of vestibular information in sensory reweighting 1



Individual with mTBI exhibits lower peak angular velocity of the head during left and right turns of various angles 2



Left to right: ABF system, ABF training during static balance exercise with head turns, ABF training during dynamic balance walking exercise 3

We have hired and trained all personnel, finalized protocols, received all test equipment and begun testing. We have tested 17 control subjects, 2 mTBI and had 5 return for 6 week follow ups.

The figures above show 1) normative values for sensory reweighting under varying sensory conditions and abnormal use of vestibular information from a single mTBI subject, 2) the single mTBI subject exhibiting consistently lower peak angular velocity of the head during turns despite similar overall gait speed to controls, and 3) the ABF rehabilitation system that detects anterio-posterior (AP) and medio-lateral (ML) linear accelerations near the body's CoM and gives feedback via sound and changes in pitch.

Goals/Milestones

CY15 Goal – Study set up and launch
- ☑ All IRB, finalize protocols, order and test all equipment
- ☑ Hire and train personnel
- ☑ Begin balance assessment (study I)
- ☐ Begin balance rehabilitation (Study II)

CY16 Goals – Characterize mTBI balance deficits and rehabilitation
- ☐ Continue testing subjects with mTBI for balance and central sensory integration
- ☐ Continue rehabilitation

CY17 Goal – Characterize mTBI balance deficits and rehabilitation
- ☐ Continue balance assessments assessments
- ☐ Continue rehabilitation trial

CY18 Goal – Complete all testing, analysis and dissemination of results
- ☐ Complete rehabilitation trial and complete all long term follow testing
- ☐ Analyze results and disseminate findings

Comments/Challenges/Issues/Concerns
- The VA is behind on their billing so we have 5 months of VA salary that has not yet been billed to the grant. We expect this to be 21,613 of VA employee time.

Budget Expenditure to Date

Projected Expenditure: $533,000.00
Actual Expenditure: $230,414.44